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AN EVALUATION OF DRUG-RESISTANT TB TREATMENT SCALE-UP

MEDECINS SANS FRONTIERES

Partners In Health

TAG
Treatment Action Group

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About the organizations

Médecins Sans Frontières (MSF) is an international emergency medical relief organization that provides direct medical assistance in over 70 countries worldwide. In 2010, MSF supported the treatment of over 25,000 TB patients across 28 countries.

Partners in Health (PIH) is an organization dedicated to providing comprehensive health care to disadvantaged populations in twelve countries around the world, including MDR-TB care in Haiti, Peru, Russia, Kazakhstan, Rwanda, Malawi and Lesotho.

The Treatment Action Group (TAG) is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS. TAG works to ensure that people with HIV receive life-saving treatment, care, and information. TAG's programs focus on antiretroviral treatments, HIV basic science and immunology, vaccines and prevention technologies, hepatitis, and tuberculosis.

Glossary

DFID	Department for International Development
DR-TB	Drug-resistant tuberculosis
DST	Drug sensitivity testing
FIND	Foundation for New Diagnostics
GDF	Global Drug Facility
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLC	Green Light Committee
GLI	Global Laboratory Initiative
MDR-TB	Multidrug-resistant tuberculosis
MOH	Ministry of Health
MSF	Médecins Sans Frontières
NTP	National Tuberculosis Programme
PIH	Partners In Health
RNTCP	Revised National Tuberculosis Control Programme
TAG	Treatment Action Group
TB	Tuberculosis
USAID	United States Agency for International Development
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

Introduction

Globally in 2008 there were an estimated 440,000 cases of incident multidrug-resistant tuberculosis (MDR-TB). Despite international calls for action to reach universal access to TB treatment by 2015, governments and ministries of health in high-burden countries have not adequately progressed with scale-up.[1,2] According to latest estimates from the World Health Organization (WHO), only 7% of the estimated MDR-TB cases in 2008 were reported (29,423) to WHO, and about 1% of patients were enrolled under programmes to provide internationally quality-assured treatment.[2] Of the 27 countries considered to have a high burden of MDR-TB,[2] only 13 reported treatment outcomes.[1]

In May 2009, the World Health Assembly adopted a landmark resolution calling on all 193 member states to urgently scale up treatment and control of drug-resistant tuberculosis (DR-TB).[3] In addition to basic control, the resolution called for the mobilisation of domestic and international resources and for countries to remove financial barriers, ensure trained and sufficient human resources, establish a network of laboratories where rapid tests are available, ensure availability of quality drugs, regulate the use of all anti-TB drugs, and introduce infection control measures. According to the WHO, this would require bold and radical policy change.[4]

Despite these political commitments, substantial funding and implementation gaps remain at both national and international levels. The Stop TB Partnership estimates that US$7.1 billion is needed to treat MDR-TB and another UD$0.3 billion is needed for laboratory strengthening for the period of 2011-2015.[5] The call for a more effective response nationally and internationally could not be more urgent.

In response to these challenges, over the past decade a number of multilateral global initiatives have been established to support drug procurement, laboratory capacity, and monitoring and evaluation of national MDR-TB programmes. Chief among these are the Green Light Committee (GLC), the Global Drug Facility (GDF), and the Global Laboratory Initiative (GLI). Established in 2000, 2001 and 2007 respectively, these initiatives are essential elements in the international MDR-TB response architecture. None has been publicly evaluated.

This report, written by Médecins Sans Frontières (MSF), Partners In Health (PIH), and the Treatment Action Group (TAG) – organisations involved in efforts to increase access to treatment and care for patients with DR-TB – aims to provide an assessment of the effectiveness of some key structures within the global response for MDR-TB, to provide recommendations on how the global response to DR-TB scale-up can be improved, and to examine the results of scale-up activities to date in three key countries. It is meant to be a first step towards greater accountability from countries, international mechanisms and donors, all of whom must work collaboratively to address the substantial barriers to scaling-up MDR-TB treatment. Currently, the GLC and GDF are being reformed to address some of the challenges highlighted in this report. It is hoped that this report will constructively inform the debate about how best to foster the scale-up of DR-TB treatment and prevention.

Methodology

This report summarises progress and challenges in MDR-TB scale-up in key countries – India, the Russian Federation and South Africa – provides an evaluation of the effectiveness of global initiatives to support scale-up, and summarises the available data on donor commitments to scale up.

Country profiles summarize publicly available data about numbers of MDR-TB patients diagnosed and treated in three middle-income, high-burden MDR-TB countries –India, the Russian Federation, and South Africa. These three countries were chosen as representing a number of challenges common to DR-TB scale-up in resource-constrained settings. Data on country-level scale-up of DR-TB services from publicly available sources is complemented by information gathered by civil society partners who collected data via structured interviews with a purposive sample of MDR-TB patients and healthcare workers, both at health facilities and within the national TB programme.

Global initiatives were evaluated by survey questionnaires sent to representatives of the global mechanisms, supplemented by publicly available data, including annual reports produced by the GLC, GDF and GLI. Questions submitted to each of these initiatives are detailed in the Appendix. Each mechanism was graded on transparency and effectiveness. All grading decisions were made upon reaching consensus among the organisations involved in writing the report, and based on the above data. All initiatives were provided with a pre-publication copy of the relevant sections of this report to allow for factual corrections and feedback.

International donor commitments were assessed by survey questionnaires sent to the following organisations: the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), UNITAID, the United States Agency for International Development (USAID), the UK Department for International Development (DFID), and the World Bank.

TB consultation in Chhattisgarh, India

Country profiles

The ultimate responsibility for scaling up MDR-TB treatment programmes lies with national governments, though many countries need international support to meet this responsibility. This report draws on publicly available information to highlight progress towards scale-up in three countries: India, South Africa, and Russia.

India

According to the WHO, India has two million TB cases every year – the highest burden of TB in the world.[6] The disease is among the leading infectious causes of mortality in India, responsible for more than 331,000 deaths in 2007. The WHO estimated that the proportion of MDR-TB was 2.3% among new TB cases and 17.2% among previously treated TB cases in 2008.[2] Altogether, about one in 20 incident cases of TB (99,000 cases) is MDR-TB, which means that India produces about a quarter of global MDR-TB cases.[2]

TB and MDR-TB financing in India

	2011
NTP Budget[7]	
Total NTP budget	US$151 million
NTP funding gap	US$31 million
% of NTP budget funded from domestic sources	27%
MDR-TB financing component[1]	
Total MDR-TB budget	US$55 million
MDR-TB funding gap	US$3 million
Contribution of gov't to MDR-TB budget (incl. loans)	US$6 million

Current status of MDR-TB treatment scale-up in India

The government of India has declared a high-level political commitment to scaling up laboratory and treatment capacity to combat MDR-TB. In 2009, the Revised National TB Control Programme (RNTCP) goals were revised to meet the following ambitious targets:[8]

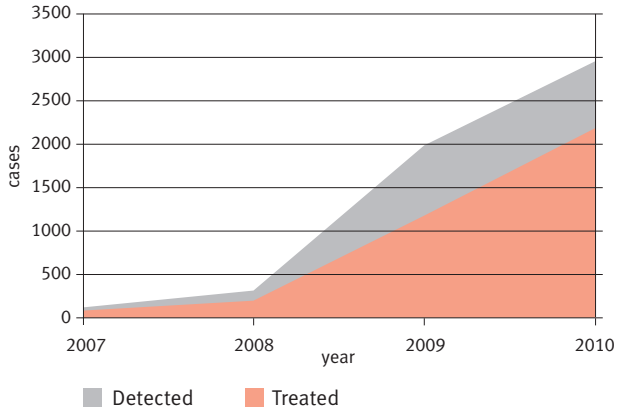
- Access to laboratory-based MDR-TB diagnosis and treatment for all smear-positive retreatment cases by 2012;
- 30,000 MDR-TB cases initiated on treatment annually by 2014;
- Access to laboratory-based MDR-TB diagnosis and treatment for all registered smear-positive TB cases by 2015.

Progress towards these targets has been slow. In 2010, 2,178 MDR-TB patients were reported to have started treatment, representing approximately 2% of the number of estimated incident cases that year.[9] There are almost no publicly available data on MDR-TB treatment outcomes. Community-based care for MDR-TB patients supported by trained, supervised, and paid community workers has been initiated in only two of 28 states.[10]

Contribution of the global initiatives in India

India submitted its first application to the GLC in 2006 with the goal of having 24 GLC sites enrolling and treating 5,000 new MDR-TB patients annually by 2011. There are several Indian pharmaceutical producers of second-line TB drugs, but not all of these products have been prequalified by the WHO. The rationale for the GLC application, therefore, was to procure quality-assured drugs through the GLC/GDF mechanisms. The majority of MDR-TB patients in India were receiving non-GLC drugs, the procurement of which was supported jointly by the World Bank and Government of India using national drug procurement procedures. India submitted an application to expand its GLC-approved MDR-TB programming in January 2010, with the goal of assuring that MDR-TB patients treated at GLC sites would receive quality-assured second-line TB drugs procured through the GLC/GDF mechanism, and financed by the Global Fund and UNITAID.[11] The RNTCP does not report on the relative proportion of GLC patients vs non-GLC patients, but in previous years non-GLC patients have been in the majority.

MDR-TB detection and treatment in India[9]

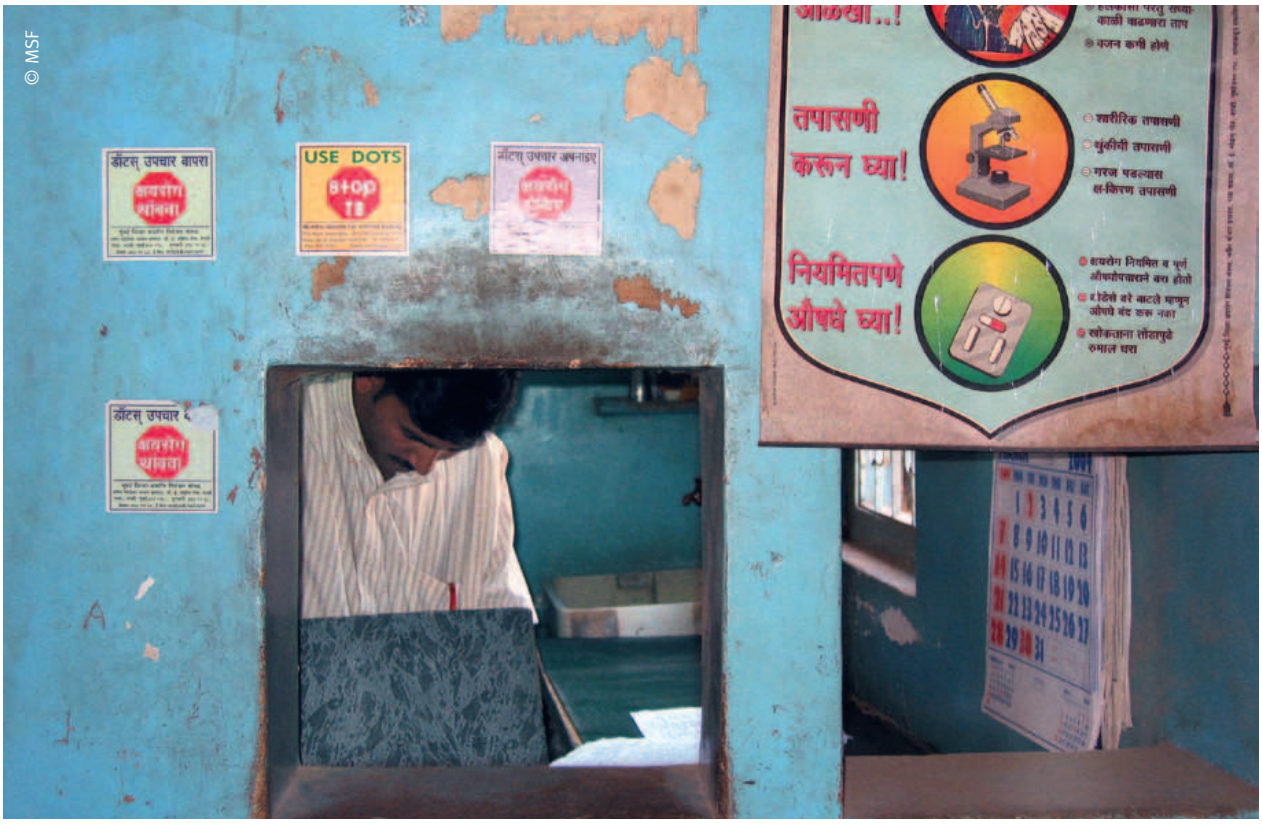


Laboratory capacity building in India

Another important bottleneck to MDR-TB treatment scale-up in India is the lack of access to laboratory diagnosis of MDR-TB. India's first GLC application in 2006 proposed an initial goal of 24 quality-assured and accredited state-level intermediate reference laboratories capable of performing TB culture and drug susceptibility testing (DST).[11] By 2011, 23 intermediate reference laboratories had been accredited for culture and DST by the RNTCP.[12]

Patient and provider perspectives in India

Patients and healthcare workers interviewed for this report stated there were often considerable delays of several months or more for drug sensitivity testing, usually after one or several failed courses of TB treatment. Patients reported inadequate support beyond the provision of drugs, for example in the management of side effects. Concern was expressed about the government's lack of willingness to admit to, and so provide treatment for, the growing number of cases of extensively drug-resistant tuberculosis (XDR-TB) in India. Patients also raised concerns about conditions in health centres, including poor hygiene, lack of infection control, and poorly integrated services that require patients to travel long distances between centres for consultations, laboratory results and medication. Discrimination was also a repeated concern, at the workplace, in the community, and even in the health centres.



TB drug dispensing facility in Mumbai, India

Russian Federation

The Russian Federation has the eleventh highest rate of TB in the world, with an estimated incidence of 106 TB cases per 100,000 population as of 2009, representing an estimated 150,000 new cases of TB that year, according to WHO calculations.[13] TB control in Russia faces substantial challenges, including low case-detection rates, especially for sputum smear-negative cases, and low treatment success rates. For MDR-TB specifically, Russia faces extreme challenges, with the third largest number of MDR-TB cases in the world as of 2009.[14,13]

According to the Ministry of Health and Social Development, 26.5% of all registered respiratory TB cases (new, retreatment and chronic cases) in Russia had MDR-TB in 2009, a proportion that has been growing every year – from 21.4% in 2007 and 23.4% in 2008. This proportion exceeded 20% in 23 of 83 federal subjects (regions), with rates as high as 32% in some regions, especially in the northwest part of the country.[14] Due to reporting methods, there are no existing indicators for the proportion of MDR-TB among all types of re-treatment cases. However, the WHO estimates that 42.4% of previously treated cases in Russia had MDR-TB in 2008.

In general, the high reported proportions of MDR-TB among new cases in several regions has prompted the Russian Federation to revise their national TB control strategy to pay particular attention to drug resistance.[13] The Russian government contributes the majority of the NTP budget (see table below). Russia received Global Fund Round 4 monies of US$88 million, and has been approved for phase 1 Round 10 monies of US$63 million.

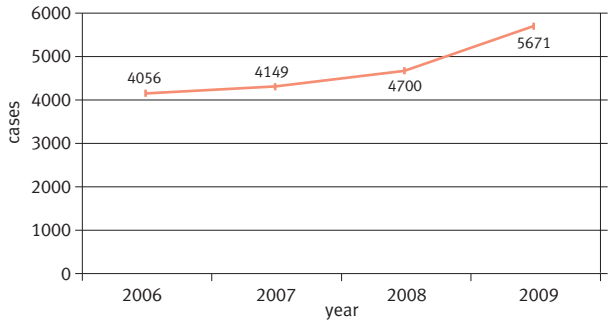
TB and MDR-TB financing in Russia

	2011
NTP Budget[15]	
Total NTP budget	US$1,278 million
NTP funding gap	US$0
% of NTP budget funded from domestic sources	99%
MDR-TB financing component[1]	
Total MDR-TB budget	US$132 million
MDR-TB funding gap	US$0
Contribution of gov't to MDR-TB budget (incl. loans)	US$127 million

Current status of MDR-TB treatment scale-up in Russia

Second-line TB drugs have been available for many years in Russia. However, the number of registered MDR-TB cases, while growing, continues to be less than the expected burden of disease. In 2009, 5,671 new MDR-TB cases were registered among new TB cases, and 2,314 new MDR-TB cases were registered among previously treated TB cases.[14] At the end of 2009, the total number of MDR-TB patients awaiting treatment was 29,031.[14] As of January 2010, the cumulative number of patient treatments approved by the GLC was 11,526; this figure does not include the number of patients enrolled in Ministry of Health (MOH)-supported programmes, which is not reported. According to the WHO, less than 30% of the estimated number of MDR-TB cases among notified TB patients were enrolled on treatment by the end of 2009.[1]

New MDR-TB cases registered among new TB cases in Russia[14]



Laboratory capacity building in Russia

In comparison to India or South Africa, Russian laboratory infrastructure is significantly more developed, with 272 laboratories providing first-line DST in 2008. However, for the most part the quality of these laboratories is not known. According to the Russian Ministry of Health, 91.4% of all new smear-positive TB cases and 90% of relapse cases receive culture and DST.[14] However, rapid methods of DST such as MGIT or line probe assay, already endorsed by the WHO and available in other parts of the world, are not generally available in Russia. Currently the majority of DST in Russia is done on solid media; culture and DST on liquid media are not officially endorsed by the NTP. In such circumstances, patients have to wait for two to three months to receive DST results, during which time they do not receive appropriate treatment and may transmit resistant strains to others. The limited availability of rapid diagnostic methods likely contributes to slow and low MDR-TB detection rates.

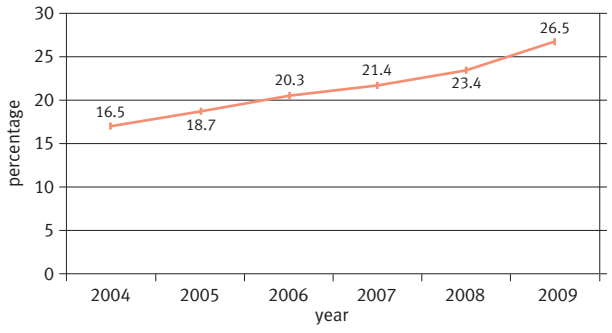
TB hospital, Russia

Treatment outcomes in Russia

According to government statistics, in the 2007 cohort of new smear-positive TB cases, the default rate was close to 10%, and the treatment success rate was only 58%[16] – the lowest officially reported rate among high-burden countries.[13] In some regions such as Siberia and the Russian Far East, treatment success was as low as 45.6% with an 18.2% default rate. Primary transmission of DR-TB is likely to be one of the factors leading to poor treatment outcomes of first-line TB treatment in some regions.

There are limited data concerning outcomes of MDR-TB treatment. In 2009, the smear conversion rate among MDR-TB patients in Global Fund projects was reported to be 63%.[17] Alarmingly, publicly available data shows an increasing proportion of MDR-TB among all registered patients with respiratory TB, indicating that ongoing transmission of MDR-TB remains a major problem. Russia also uses some non-standard regimens for treatment of Category I failures that are not endorsed by the WHO and the GLC. An area of concern is the presence of the Russian Category 2B regimen for MDR-TB suspects in the national guidelines. This regimen adds an injectable agent and a fluoroquinolone (+/- ethionamide) to ethambutol and pyrazinamide. Although its use is being debated at the level of the five Russian TB Research Institutes, it continues to be used in a number of Russian Oblasts. Both diagnosis and treatment of DR-TB needs to be improved before a favourable impact on the epidemic can be expected.

Percentage of MDR-TB in registered patients with respiratory TB in Russia[14]



Contribution of the global initiatives in Russia

The GLC plays a major role in MDR-TB response in the Russian Federation. As of May 2010, 11,526 patients have been approved in 31 different GLC-approved projects.[18] This represents a rapid scale-up of GLC-approved projects in recent years. As in India, however, there are also substantial numbers of patients who do not receive quality-assured drugs from the GLC/GDF mechanism, but the exact numbers of such patients are not publicly available. The most recent Global Fund scorecard (April 2010) noted that the Russian grant reached the majority of its targets with the exception of initiating treatment for MDR-TB. The Global Fund cited global drug shortages of MDR-TB drugs as the main reason for Russia's lack of MDR-TB treatment initiation, stating that the country itself should not be held accountable.[17]

Patient and provider perspectives in Russia

Health providers identified insufficient funding for TB programmes as a major obstacle to accelerating access to TB services. Other challenges included stockouts of second-line TB drugs, and a lack of access to modern methods of rapid detection of TB and drug resistance. Patients raised the lack of availability of drugs to treat DR-TB as a primary concern. The lack of psychological and social support, including treatment for people who use drugs and/or alcohol, was another expressed concern. Support for patients to adhere to and complete treatment for MDR-TB depends largely on the availability of treatment for substance abuse, since many patients have problems with drugs and alcohol, and hospitalisation for DR-TB treatment without such supportive services means requiring patients to abruptly commit to being drug and alcohol-free. Patients also emphasised the poor state of TB facilities: infrastructure in disrepair, overcrowded rooms, and inadequate infection control. This is particularly concerning given the great reliance on hospital-based management for DR-TB.

South Africa

In 2009 South Africa had the world's third highest TB burden and its fifth highest MDR-TB burden. The estimated TB incidence rate for South Africa is 948 cases per 100,000 population, with approximately 500,000 new cases in 2009. An estimated 73% of new TB patients are co-infected with HIV, and approximately 31% of all TB/HIV patients in Africa are in South Africa.[19] The WHO estimated that the proportion of MDR-TB was 1.8% among new TB cases and 6.7% among previously treated cases in 2008.[2] Altogether, approximately 3% of incident total TB cases (13,000) are estimated to have MDR-TB.[2]

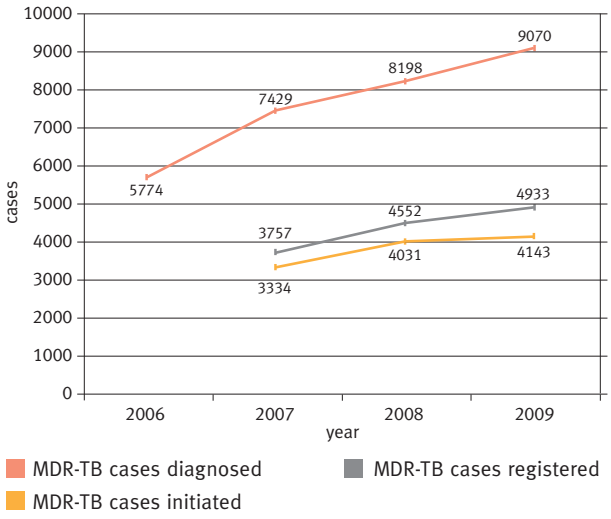
TB and MDR-TB financing in South Africa

	2011
NTP Budget[20]	
Total NTP budget	US$436 million
NTP funding gap	US$0
% of NTP budget funded from domestic sources	75%
MDR-TB financing component[1]	
Total MDR-TB budget	US$238 million
MDR-TB funding gap	US$0
Contribution of gov't to MDR-TB budget (incl. loans)	US$238 million

Current status of MDR-TB treatment scale-up in South Africa

In 2008, of approximately 13,000 incident cases of MDR-TB, over 6,000 were diagnosed.[2] This relatively high proportion of diagnosed cases compared to other countries in the region reflects efforts made to expand access to laboratory testing: currently, there are 15 laboratories performing culture and ten laboratories performing first-line DST.[2] However, the last South African national survey of MDR-TB prevalence was carried out in 2001 and true incidence estimates may be much higher.

MDR-TB cases in South Africa[22]



Treatment outcomes and decentralised management of MDR-TB in South Africa

Outcomes are significantly worse for MDR-TB treatment (cure plus completed 42%)[21] than for all new smear-positive TB cases (76%)[20] in South Africa. This is partly due to the high proportion of TB/HIV co-infection in South Africa compared to other counties. Following results from pilot studies, the NTP has adopted a strategy of decentralised management of MDR-TB. This strategy focuses on supporting ambulatory and community-based care for MDR-TB by increasing the numbers of MDR-TB units, mobile injection teams, and community treatment supporters.[22] However, centralised, hospital-based management remains the norm.

Contribution of the global initiatives in South Africa

The GLC/GDF mechanism does not play a significant role in South Africa. As of May 2010, there were no GLC-approved sites in South Africa. Most second-line TB drugs in South Africa are produced domestically and are not quality assured according to international standards.

Patient and provider perspectives in South Africa

Providers noted that there have been significant efforts at scaling up MDR-TB treatment over the last decade. The use of weak standardised regimens may lead to amplification of drug resistance and the emergence of XDR-TB. The policy of keeping some (mostly expensive) drugs in reserve for XDR-TB treatment may actually contribute to more XDR-TB, as patients are not always provided with maximally effective combination therapy. Concern was also expressed about the lack of capacity to do DST, as the high caseload of TB has overwhelmed currently available diagnostic capacity. Concern was expressed that limited budgets are further stretched because South Africa is not accessing the best internationally available prices for DR-TB drugs. South Africa has ambitious plans to roll out Cepheid GeneXpert MTB/RIF testing nationally. The impact of this new technology on increasing access to treatment for smear-negative and MDR-TB patients has yet to be seen. Another area of concern is infection control, which is still not considered a priority, while environmental and administrative controls are implemented inconsistently. Finally, the focus on hospitalisation for all DR-TB patients for initiation of treatment has led to poor access to treatment, long waiting lists, high treatment default which contributes to poor outcomes, and further community transmission of TB due to poor access to effective MDR-TB services. Pilot programmes have been established in several sites to evaluate the effectiveness of decentralised DR-TB management, but centralised care continues to dominate, and government commitment to decentralised care needs to be further strengthened.

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TB patients in the MSF-supported programme in Khayelithsa, South Africa

The global initiatives

This section provides an overview of the performance of the three main international mechanisms that support countries to scale up MDR-TB diagnosis and treatment: the Green Light Committee (GLC), the Global Drug Facility (GDF) and the Global Laboratory Initiative (GLI). Initiatives have been graded from A (excellent) to F (poor). A grade of I was awarded in the case of incomplete information.

The GLC is currently undergoing reform and the GLI and GDF are also making changes in how they operate to address some of the challenges highlighted in this report. The information provided in this report is valid up to 31 June 2011.

Green Light Committee (GLC)

The GLC initiative was launched in 2000 in order to increase access to second-line drugs for DOTS-Plus pilot projects which meet a minimum set of quality standards. It consists of the Green Light Committee (GLC) and the Global Drug Facility (GDF). The GLC initiative includes the Stop TB Partnership which houses the GDF, and the WHO, as well as other implementation, funding, and technical assistance partners. The GLC has four key functions:[23,24,25]

- Reviewing applications from countries that wish to benefit from quality-assured, second-line anti-TB drugs at reduced prices through the GDF;
- Promoting technical assistance to countries throughout the application and implementation processes;
- Monitoring and evaluating GLC-approved programmes to assess their progress and continued adherence to WHO guidelines;
- Informing the WHO of GLC findings, deliberations and recommendations, and assisting the WHO with developing policy to control MDR-TB.

The Green Light Committee must approve proposed projects in order for them to receive funding support from the Global Fund or from UNITAID. Countries wishing to receive such support submit a standard application form available on the GLC website. The GLC also facilitates access to technical assistance that is coordinated by WHO and its technical partners. This includes pre-application planning, pre-application site visits, and regular monitoring missions to evaluate project performance. Finally, GLC approval provides access to concessionary-priced quality-assured second-line drugs via the GDF mechanism. GDF drugs are not available to projects that have not been approved by the GLC.

The largest donor to the GLC is the Global Fund, followed by USAID and UNITAID. According to the 2009 annual report, the budget was used for WHO GLC secretariat costs (37%), partners' contracts (including technical assistance) (29%), GLC regional services (14%), programme support costs (13%), and GLC operations and meetings (7%).

The GLC initiative[26]

GLC operating budget, 1 Jan 2008-31 Dec 2009[27]

Donor	Income (US$)	Percent
USAID	1,825,744	35%
GFATM	2,675,000	51%
UNITAID	502,801	10%
Eli Lilly	160,424	3%
WHO (regular budget)	57,764	1%
Total	5,221,733	

Transparency: A

The GLC maintains a high level of transparency with respect to its activities. The GLC's Annual Report 2009 provides a detailed explanation of almost every aspect of the GLC, including overall strategy, budget/expenditures, the number of approved programmes and the number of patients supported through those programmes.[28] The GLC was responsive to requests for additional information not contained in the publicly available documents. We sent a list of questions (see Appendix) and received prompt and detailed answers to all of them.

Effectiveness: D

In the ten years since its launch, the GLC has instigated a number of policy successes, but the number of patients treated by GLC-approved programmes is low in comparison to the need. By the end of 2010, approximately 29,500 patients (of an estimated five million new MDR-TB patients globally since 2000) were reported enrolled in 55 countries and 85 GLC-approved programmes. Even with GLC and donors' approval, countries were only able to enrol about 50% of the MDR-TB patients who had been approved.[27] Furthermore, MDR-TB patients receiving non-GLC drugs continue to outnumber those receiving GLC drugs by a considerable margin. Since non-GLC drugs are not quality-assured, this does raise the question of whether the GLC mechanism has been able to sufficiently increase access to quality treatment for MDR-TB patients globally. The greater proportion of patients on non-GLC vs GLC-approved drugs is also a measure of the difficulties and lack of incentives that countries experience in getting access to quality-assured drugs.

The time and effort required by the GLC application process is a concern. Since GLC approval is required by both the GFATM and UNITAID, the application process is an additional barrier to external funding, and one that is unique to MDR-TB. The GLC stated that a preliminary analysis of fast track and regular applications received between January 2007 and July 2009 shows that the mean lead time from receipt of application to approval by the committee is 106 days, with certain fast track applications approved within two days; this does not include the time required by countries to write the application. The WHO's GLC Application Instructions explains that an application to the GLC requires a cover letter and the completion of 15 sections, including information on DR-TB in the area and past use of second-line drugs, government commitment and partnerships, laboratory aspects, treatment delivery and adherence, patient rights and responsibilities, and information systems and management.[29] Some countries require technical assistance from outside consultants to develop their action plan which results in additional costs and delays.

The GLC's poor effectiveness grade takes into account the fact that this entity was not created and designed for the scale-up of national DR-TB treatment programmes, but for the technical support and monitoring of pilot projects. The GLC has had a limited impact on the overall global effort to scale-up DR-TB diagnosis and treatment. Despite being influenced by multiple factors, the scale up of DR-TB diagnosis and treatment is ultimately a marker of the GLC's ability to promote effective technical assistance to build country capacity to implement DR-TB programmes.

Many of the first DR-TB pilot projects were organised within the GLC mechanism. At the current time, however, most DR-TB patients are either not treated at all, or treated with drugs and regimens of unknown quality, either in countries that do not participate in the GLC mechanism, or else in parallel non-GLC programmes even in the countries that do have GLC-approved projects. In such an environment, while the GLC does help create a baseline quality standard and help direct national DR-TB policy, it is clear that another type of support to countries is needed. The GLC does provide technical assistance for GLC-approved programmes. However, a comprehensive evaluation of the quality of this technical assistance has not been done, and was beyond the scope of this report.

The GLC is currently undergoing a reform process but it has yet to be seen if the revised GLC structures will provide more effective support to DR-TB scale-up.

Global Drug Facility (GDF)

The Global Drug Facility (GDF) was founded in 2001 as part of the Stop TB Partnership, with a mandate to oversee procurement of first-line TB medications to enable stable low prices and quality assurance, and to prevent stockouts. Since its inception, the GDF reports that it has delivered first-line TB treatments for 16.5 million people; 2.4 million of these were delivered in 2009.

At the end of 2006, the GDF assumed responsibility for procurement of second-line TB drugs for GLC projects. Projects generally place orders for second-line drugs with the GDF which then forwards them to its procurement agent. The GDF tracks orders, monitors the performance of the procurement agent, compiles forecasts of future drug needs, and negotiates with suppliers interested in being added to the GDF's approved suppliers list.

The stated objectives of the GDF are:[30]

1. To make the purchasing of TB drugs more cost-effective and timely;
2. To improve quality of anti-TB drugs around the globe;
3. To prevent the emergence of new strains of drug-resistant TB;
4. To provide in-country assistance on drug management, registration and supply issues.

Transparency Grade: B

The GDF provides fairly detailed information about the number and kind of country applications approved, including the country, type of grant, number of patients, and total estimated cost for all country reviews. Prices of second-line drugs procured by the GDF are available at the WHO Global Price Reporting Mechanism.[31] This data is available only since 2007, however, when the GDF took over procurement of second-line drugs for GLC-approved projects.

There is less information about the number of suppliers. When asked when specific drugs became available for procurement via the GDF, the GDF responded that no such date could be provided as this depended on registration status in each particular country. Finally, it was not possible to obtain relevant data about the timeliness of GDF procurement. The GDF notes a lead time (defined as "date firm order is placed with procurement agent until first shipment received in country")[30] of approximately three months for delivery of second-line drug orders. However, a more relevant metric for timeliness would be the time required for all ordered drugs to arrive in the country. Since drugs may be shipped as soon as they are available, the lead time of some drugs may be less than others. Given that a full regimen is required for effective treatment, the lead time of the first shipment may not be an accurate metric of the delay until treatment can be started.

Effectiveness Grade: D

The GDF's first stated objective is "make the purchasing of TB drugs more cost-effective and timely." In 2010, the International Union Against Tuberculosis and Lung Disease and MSF published a report DR-TB Drugs Under the Microscope, which showed that four of the seven drugs that GLC was procuring had increased in cost by anywhere from 292% to 991% over the last decade, since 2001.[32]

The GDF stated that a number of factors need to be taken into consideration, such as different or non-existent quality assurance policies. In 2001, the GDF was not procuring any second-line drugs, and quality assurance standards of medicines were unknown to the GDF at that time. The GDF started to procure second-line drugs in 2007 with one supplier of second-line drugs in the majority of the cases since the market was under-developed at that time. The GDF further asserted that price fluctuations were dependent on currency exchange, increase of energy and other manufacturing costs, and investments in prequalification. The GDF provided the following table comparing prices of second-line TB drugs from 2008 to 2011.

Product	Description	Supplier	2008 price (US$)	2011 price (US$)	Price change
Amikacin	500 mg/2 mg injectable vial, pack(s) of 10 vials	Medochemie	$14.33	$12.80	-11%
Capreomycin	1 g powder for inj, 1 vial*	Eli Lilly	$3.00	$4.00	33%
Cycloserine	250 mg, pack of 100 capsules	MacLeods	$47.63	$59.29	24%
Ethionamide	250 mg, pack of 100 tablets	MacLeods	$9.54	$8.53	-11%
Kanamycin	1 gr powder for inj, 50 vials	PanPharma	$31.01	NA from this source	
Levofloxacin	250 mg, blister pack 100 tablets	MacLeods	$4.86	$5.00	3%
Levofloxacin	500 mg, blister pack 100 tablets	MacLeods	$8.06	$7.85	-3%
Ofloxacin	200 mg, pack of 100 tablets**	Macleods	$3.26	$5.70	75%
Prothionamide	250 mg, pack of 100 tablets	Fatol	$15.39	$15.01	-2%
PASER	4 gr granules, pack of 30 sachets	Jacobus	$55.22	$47.00	-15%
Moxifloxacin	400 mg, pack of 5 tablets	Bayer	$24.50	$15.77	-36%

* Concessional pricing, no negotiations
** Phasing out during 2010/11 due to changes in guidelines.

This table is not compelling evidence that second-line drugs have become more cost-effective overall. Since 2008, some drugs have decreased in price, but others have increased significantly in price. The GDF argues that price reductions should not be the primary measure of their success – the more critical issue is to ensure sufficient manufacturers of second-line drugs to keep prices stable. Despite these claims, both the number of manufacturers and prices of second-line drugs do not appear to be optimal to ensure access to quality-assured drugs.

Global Laboratory Initiative (GLI)

The GLI, launched at the end of 2007, is one of seven working groups of the Stop TB Partnership. As with other working groups, it is overseen by a core group of 16 members who act as a steering committee to guide, evaluate, approve, support and facilitate GLI activities. The overall goal of the GLI is to facilitate scale-up of TB laboratory services. It has a global network of partners, including donors, national agencies, private foundations, scientific organisations, TB control programmes and technical expert groups, all dedicated to TB laboratory strengthening. A secretariat, hosted by the WHO Stop TB Department, provides strategic guidance, supports the governance of GLI, facilitates coordination of GLI priority projects, and serves as the focal point for TB laboratory strengthening activities at WHO headquarters. The GLI reported that the budget in 2009 was US$3,277,000. The GLI stated that around 40% of the GLI budget is for Geneva expenses, including staff salary as per formal WHO agreements, and GLI administrative expenditures (meetings, stakeholder liaison, policy development and resource mobilisation).

The EXPAND-TB Project (Expanding Access to New Diagnostics for Tuberculosis), started in 2009, is one of GLI's most important projects. EXPAND-TB is a partnership involving the GLI, the Foundation for New Diagnostics (FIND), and the GDF, and is funded by UNITAID at a cost of US$87.5 million for commodities (laboratory equipment and supplies) up to 2013. The WHO secretariat of GLI is responsible for project oversight and normative guidance, while FIND and the GDF are responsible for technical assistance and procurement, respectively. EXPAND-TB is targeting 101 laboratories in 27 low and low/middle-income countries in a phased fashion depending on country readiness and availability of non-commodity resources. The GLI focus countries include: Lesotho, Ethiopia, Cote d'Ivoire, Myanmar, Democratic Republic of Congo, Uzbekistan, India, Azerbaijan, Georgia, Kazakhstan, Moldova, Tajikistan, Belarus, Peru, Tanzania, Haiti, Djibouti, Uganda, Cameroon, Zambia, Senegal, Kenya, Swaziland, Bangladesh, Indonesia and Vietnam.

GLI Structure and Governance

WHO Stop TB Department **GLI Secretariat**	**Stop TB Partnership**
GLI Core Group	Evaluates, approves, governs projects; Advises GLI Secretariat
GLI Partners Committee	Advises and approves strategic agenda of GLI; Monitors project progress

Technical Working Groups	**Laboratory strengthening roadmap**	Priority projects and activities Time limited Partner approach
	Human resource development strategy	
	Laboratory biosafety	
	Laboratory accreditation	
	Other	

Transparency: D
While there is a wealth of publicly available information about the GLI's structure, governance, operating procedures and laboratory tools, the GLI has not published any progress reports on its activities since its inception in 2007. Even in the context of specific, high profile projects such as EXPAND-TB, there is almost no information about actual GLI activities, performance indicators and/or outcomes.

In response to our requests for additional information about funding, the GLI provided a full list of 2009 contributions by donor. This information is not included in this report due to confidentiality agreements the GLI has with its donors. The GLI also provided information about numbers of staff members and which funders support them.

The low grade for transparency is because the GLI was able to provide only the most general information on its specific activities and whether they were successfully implemented. In response, the GLI replied that progress has been reported since 2008 in WHO annual reports, in partner reports, at international meetings and conferences (notably the annual Union World Lung Conference), and at dedicated meetings by UNITAID. Presentations and meeting reports are available on the GLI website. These reports were reviewed, and found to lack specific metrics about the laboratory capacity built in the countries targeted by GLI and EXPAND-TB.

Effectiveness: I
Though the normative work done by the GLI to clarify the utility of the Cepheid GeneXpert MTB/RIF test at the end of 2010 was impressive in its speed and clarity, the same cannot be said for the outcomes that GLI has been able to achieve since its inception in 2007. The almost complete lack of information about the nature and impact of GLI country-level activities in increasing laboratory capacity makes it impossible to evaluate its effectiveness. For this report GLI was requested to provide information about (1) improvements in the smear microscopy network, and (2) the testing capacity of specific laboratories in target countries. The GLI was unable to provide more than very general statements, such as "All EXPAND-TB countries are implementing liquid culture and DST (MGIT), rapid speciation testing and line probe assay." In response to requests for quantitative data, the GLI responded that it is not directly involved in the collection of laboratory data, but its secretariat provides input to the TB Monitoring and Evaluation team at the WHO responsible for global monitoring and evaluation.

In subsequent communications, the GLI agreed that there was a need to publicise GLI's achievements, but that due to other competing priorities this had taken a back seat. They also clarified that in most developing countries laboratories have to be physically built from scratch or require extensive renovation and refurbishment, followed by a prolonged period of training, local capacity development and on-site mentoring. Only after this effort has been completed, which can take up to two years, can new diagnostic technologies be implemented and their utility validated, including through mentoring, monitoring and evaluation, and impact assessment. As most developing countries are still in the very first phase of laboratory preparedness for MDR-TB diagnostic capacity, the efforts of the GLI can best be measured by adoption of WHO diagnostic policies and GLI standards in these countries. In conclusion, the GLI argued that it is too early to do an impact assessment.

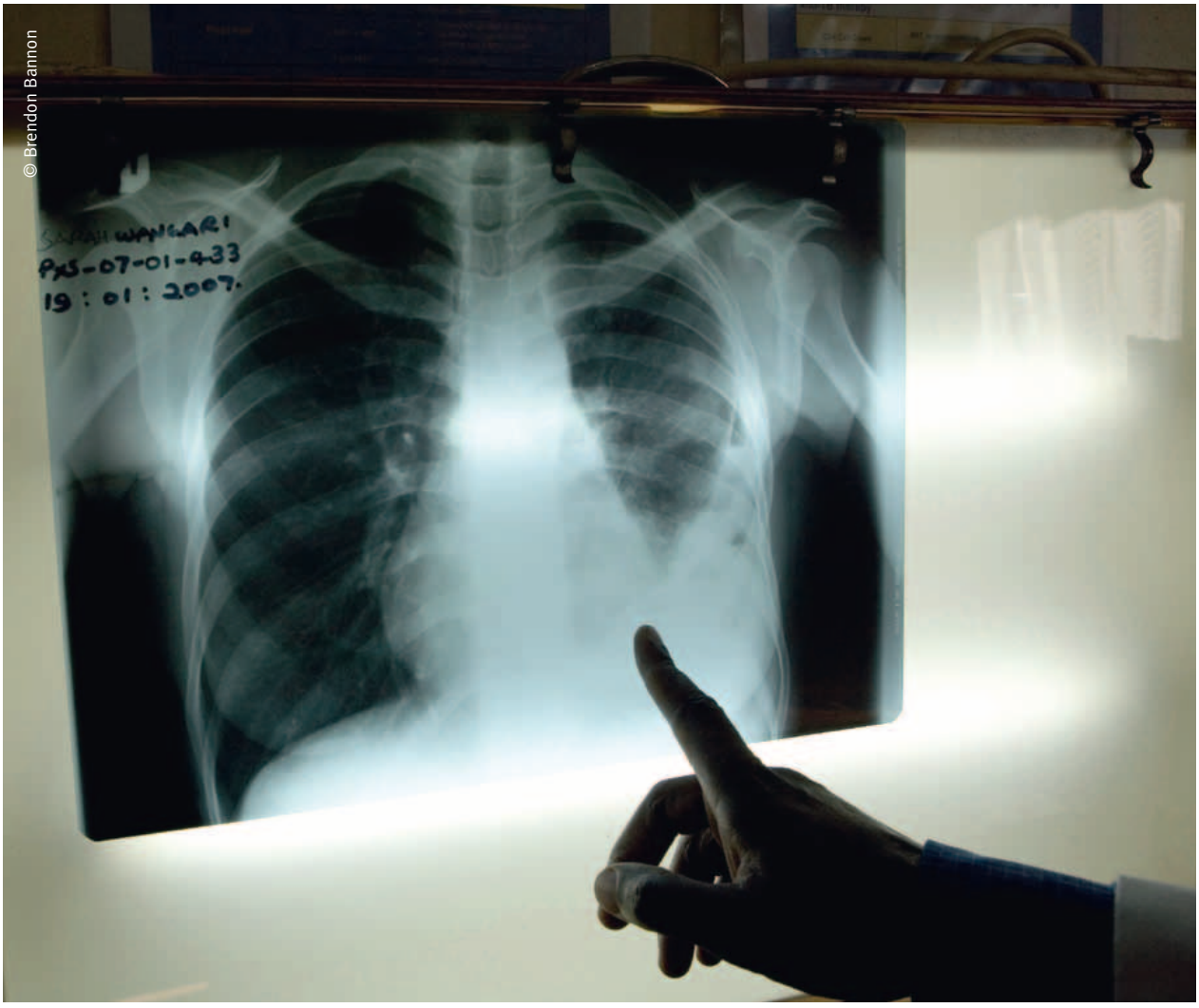
Setting up laboratory services in developing countries is clearly a major challenge. However, it is not too early for an impact assessment, as even interim measures – the capacity of countries to diagnose MDR-TB at the time of initial assessment, or what measures of increased capacity were demonstrated through the work of GLI – could also give very useful measures of GLI's success. The GLI has been operational for a relatively short time, but it is reasonable to expect to see some demonstrable increases in laboratory capacity in target countries by this time.

The lack of concrete measures of success of the GLI at country level is surprising, and targets and indicators for laboratory strengthening in the Stop TB Global Plan, 2011-15 are inadequate to monitor the effectiveness of the GLI. The GLI should be judged on its effectiveness in its target countries and against interim targets that would show its ability to reach the 2015 targets. It is strongly recommended that concrete achievements of the GLI should be collected and made publicly available on a regular basis to allow for support and advocacy and to ensure that it is fulfilling its mandate effectively.

Donor commitment to supporting scale-up of DR-TB diagnosis and treatment

The following donors were contacted using a standardised questionnaire to assess funding support specifically for DR-TB diagnosis and treatment: the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), UNITAID, the United States Agency for International Development (USAID), the UK Department for International Development (DFID), and the World Bank. All donors either did not respond to repeated inquiries, or were not willing to publicly provide specific information about DR-TB funding.

Donor	Estimated amount of funding aimed at diagnosis and treatment of DR-TB globally
GFATM	Did not respond to inquiries
UNITAID	Did not respond to inquiries
USAID	Approximately 18% of total TB budget, or US$27 million total
DFID	Unable to provide specific information
World Bank	Unwilling or unable to provide specific information



MSF doctor examines x-ray of a TB patient in Mathare, Kenya

Conclusions

Global and national scale-up to meet the enormity of the DR-TB pandemic is far from adequate. This report highlights several important failures in the global response to scaling up DR-TB care.

1. DR-TB treatment scale up does not match the caseload of patients.

2. The quality and success of the scale-up effort is poorly documented, with very limited outcome data available for the three countries reviewed in this report. Patient and provider perspectives highlight many shortcomings in programme management and infrastructure that negatively impact quality of care.

3. All countries reviewed had insufficient access to quality-assured laboratory diagnostic capacity, resulting in delays in the diagnosis of drug resistance, and an enduring burden of undiagnosed drug resistance.

4. Quality-assured drug access is limited and substantial numbers of patients are receiving drugs of unknown quality. Quality of care is further jeopardised by insufficient drug suppliers, inadequate drug regimens and stockouts.

5. Lack of political commitment, inadequate international support mechanisms, and lack of political will at both national and international levels is impeding progress at country level.

6. The adequacy of available funding against the funding targets set for MDR-TB and laboratory infrastructure recommended by the Global Plan is impossible to assess: all major donors surveyed for this report were unable or unwilling to provide specific information regarding their support to DRTB programming. Their lack of transparency may be due to insufficient priority given to this public health problem.

Recommendations

1. Countries, especially those with a high burden of DR-TB, need to scale up accessibility of diagnosis and treatment for DR-TB.

2. Quality of DR-TB care needs to be improved by addressing shortcomings with regard to factors critical for DR-TB clinical management such as diagnostics, drug supply, adherence support and infection control.

3. Countries should provide information about the quality of DR-TB drugs and treatment outcomes, not just the numbers of patients treated. Reporting of treatment outcomes, even if poor, can help direct overall global strategy and funding towards interventions that can improve DR-TB treatment programmes.

4. International support mechanisms such as the GLC, GDF and GLI should be evaluated regularly with respect to their publicly stated goals. Even as GLC and GDF undergo their transitions, interim markers of success need to be set up and their progress measured. Increasing funding is provided to these mechanisms, with very little evidence of their effectiveness. Donors, in particular, are well positioned to facilitate the transparent reporting of results from these support mechanisms in return for financial support.

5. Donors need to make scale-up of DR-TB diagnosis and treatment a clearly articulated priority, and should provide information about total funding provided for DR-TB diagnosis and treatment, as well as disaggregated information about specific interventions within this category.

6. Civil society groups have an important role to play in the monitoring of global efforts to scale up DR-TB diagnosis and treatment. These groups are particularly well-suited to monitor both access to and quality of treatment at the country level, but should also be involved in the evaluation of international support mechanisms and donor commitment. Some groups are directly involved in providing and supporting treatment and are thus an important part of the response to the epidemic.

Limitations

There are several limitations to this report. First, the lack of consistency in publicly available data from countries limits comparability and completeness. Second, the country profiles were illustrative, rather than inclusive, and as such some notable countries are missing. China in particular represents a substantial proportion of the global DR-TB burden, and many of the issues raised in this report apply to China and other high-burden countries. Future reports should include a broader set of high-burden countries. Third, the GDF and GLI were unable or unwilling to provide information about the effectiveness of their programmes; these grades were incomplete. Finally, most donors were unable to provide even basic information on specific funding for DR-TB diagnosis and treatment, and so an analysis of donor commitment was impossible.

Appendix: Questions submitted to the Global Initiatives

GLC questions

1. What was the operating budget in 2009? That is, the 2009 equivalent of Table 5 of the GLC 2008 Annual Report.
   - Who were the funders of the 2009 operating budget? How much did each funder contribute?
2. What were the expenditures of the operating budget? Table 6 (page 29) of the GLC 2008 Annual Report combines operating and procurement expenditures. The procurement budget for second-line TB drugs is much larger than the GLC operating budget. We would like to know the breakdown of expenditures for the operating budget only.
3. What proportion of the GLC 2009 operating budget was expended by WHO Geneva, and what proportion by countries and regions?
4. How many Technical assistance missions were accomplished in 2009?
5. Please provide a breakdown of the purposes of these TA missions (new GLC application, monitoring and evaluation of old GLC project etc)
6. What is the mean lead time for GLC applications, ie what is the mean number of days from the submission date until the approval date?

Open-ended questions:

7. Is there a mechanism to respond to country suggestions and complaints? Can you please give an example of how this mechanism has worked in the past?
8. How do you monitor the quality of technical assistance provided by GLC consultants?

GDF questions

1. Who is the procurement agent for MDR-TB drugs? Is it IDA?
2. You define the 'lead time' as the "date firm order is placed with procurement agent until first shipment received in country" [Progress Report 13, page 37]. However, this ignores the fact that orders are usually split into partial shipments based on availability of drugs. Can you please provide the mean 'complete' lead time, meaning the date firm order is placed with procurement agent until the last shipment received in country?
3. Annex 4 of Progress Report 13 (page 40-41) is a list of all the suppliers of second-line TB drugs.
   - What does "interim review" mean?
   - Are drugs in interim review available to countries from the GDF? We ask this because some interim review drugs appear to be listed in the GDF website, but some do not.
   - Please provide the date that each drug was available to countries for procurement via the GDF (prequalification date or interim review date, depending on the answer of previous question). Please include all suppliers of kanamycin, which seem to be omitted from Annex 4.

4. What was the lowest price available of each second-line TB drug in each year?

	2002	2003	2004	2005	2006	2007	2008	2009	2010
Amikacin									
Kanamycin									
Capreomycin									
Ofloxacin									
Levofloxacin									
Moxifloxacin									
Ethionamide									
Prothionamide									
Cycloserine									
Terizidone									
PAS									
Amox-clav									

5. With respect to the Strategic Rotating Stockpile for MDR-TB which was created in 2009:
   - What was the start-up expenditure?
   - Are there any ongoing expenditures?
   - What is the mean lead time of the 39 orders serviced by the Stockpile in 2009?
   - How many orders were serviced by the Stockpile in 2010 and what is the mean lead time?

Open-ended questions:

6. Is there a mechanism to respond to country suggestions and complaints?
7. Can you please comment on the GDF kanamycin shortage of 2009? What was the reason for the shortage? What actions has GDF taken to avoid this sort of problem in the future?
8. Do you have any opinions about the work of the International Development Association, your procurement agent for second-line TB drugs?

GLI questions

1. What was the GLI budget for 2009?
   - Please provide a breakdown of all funders, and their respective contributions to the 2009 budget.
2. Please provide a breakdown of expenditures of the 2009 budget.
   - What proportion of all expenditures was spent in Geneva?
3. How many GLI staff are in Geneva?
4. Which countries has GLI assisted since its inception?
5. Please provide data about improvements in the smear microscopy network in the countries listed in #4.

Country	Period of GLI assistance	Number of smear microscopy sites pre-GLI	Number of smear microscopy sites post-GLI

6. Please provide data about the testing capacity of specific laboratories in the countries listed in #4.

Country	Location and name of specific laboratory receiving GLI assistance	Type of laboratory method supported by GLI assistance (solid culture, MGIT, Hain etc)	Number of tests performed in last quarter of 2009
(Country)	(Laboratory)	(Solid culture)	(#)
		(MGIT)	(#)
	(Laboratory)	(Solid culture)	(#)
		(MGIT)	(#)

7. How many GLI technical assistance visits/missions were performed in 2009?
8. How many long-term GLI consultants are there? Which countries are they in?

Open-ended questions:

9. Is there a mechanism to respond to country suggestions and complaints?
10. Please explain your relationship with FIND. Has this been a satisfactory relationship? Why or why not?
11. How do you monitor the quality of technical assistance provided by GLI consultants?

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MSF doctor examines a patient x-ray in the MSF DR-TB programme in Khayelitsha, South Africa

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